Hamdy et al.
Egypt J Neurol Psychiatry Neurosurg (2022) 58:99
https://doi.org/10.1186/s41983-022-00537-y

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH Open Access

Vasomotor reactivity in patients with cerebral small vessel disease vs. internal border zone infarction and its correlation with disease outcome

Sara Hamdy[1], Mai Fathy[1*], Azza Abd Elnasser[1], Eman A. F. Darwish[2], Eman Hamid[1], Hany Aref[1,2] and Nevine El Nahas[1,2]

Abstract

Background: Available data collected from patients of different types of cerebrovascular strokes can detect risk factors, severity and clinical outcome of these patients. Differentiating between different types of strokes is mandatory for early diagnosis and proper management. The aim of this study is to compare between cerebral small vessel disease with lacunar infarctions and internal border zone infarctions regarding vasomotor reactivity by using transcranial color-coded duplex and its correlation with their MRI perfusion, disease severity and outcome.

Results: On admission, 56.7% of patients in lacunar stroke had impaired reactivity vs. 100% of patients in internal border zone group. At 3 months follow-up, this number dropped to 23.3% in lacunar group, but persisted as 100% in internal border zone group. On comparing the 3 perfusion parameters between the 2 groups, there was statistically significant impairment in all parameters in patients with internal border zone infarction than patients with lacunar infarction (longer time to peak, decreased cerebral blood flow and cerebral blood volume). By comparing the severity of the stroke by using National Institute of Health and Stroke Scale, it was found that patients with internal border zone infarction had higher disability than patients with lacunar infarction on admission and on discharge. At 3 months follow-up, the lacunar group had a better outcome than of the border zone group.

Conclusion: Patients having internal border zone infarction had higher clinical disability and worse prognosis, together with more impairment in vasomotor reactivity and MRI perfusion parameters than patients having lacunar infarction.

Keywords: Small vessel disease, Border zone infarction, Vasomotor reactivity, Perfusion, Lacunar infarction

Introduction

Cerebral small vessel disease (CSVD) is a frequent neurological condition that affects the elderly, it leads to strokes, dementia, mood swings, and gait abnormalities. The diagnosis of CSVD depends on imaging which can include white matter hyper intensities, microbleeds and lacunar ischemic strokes. However, the CSVD features may share some common characteristics with other types of stroke as border zone infarcts [1]. Border zone infarcts are ischemic lesions that occur in specific areas at the watershed zones between two main arterial territories. The most common causes of internal border zone (IBZ) infarctions are either hypoperfusion or embolism [2]. Despite the different etiologies yet both disorders can have a similar clinical presentation and share a common

*Correspondence: maifathy@med.asu.edu.eg

[1] Neurology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Full list of author information is available at the end of the article

radiological picture of white matter lesions. Moreover, if IBZ infarctions developed bilaterally they can be misdiagnosed as CSVD. Therefore, given that the management pertaining to acute intervention and secondary prevention differs among both disorders, then it is essential to find handy tools for differentiation [3].

The aim of this study is to find radiological characteristics that distinguish CSVD with lacunar infarctions from IBZ infarctions regarding vasomotor reactivity and its correlation with MRI perfusion patterns, disease severity and outcome.

Methods

Sixty patients were recruited from the stroke unit of the University hospital from August 2019 through July 2021. A written informed consent was obtained from all participants or first of kin and the study was approved by local research ethics committee FWA 000017585 in 2019. All procedures performed in the study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This is a prospective cohort observational study. The study recruited 60 patients divided into 2 groups, 30 patients with lacunar infarction and 30 patients with IBZ infarction, all patients were above 18 years of age. Patients were included in the first group if they had clinical signs of lacunar syndrome [4], no large vessel disease or cardioembolic disease. Patients with IBZ infarction in the second group were included if their MRI showed unilateral lesions in the internal border zone area with ipsilateral internal carotid stenosis (with or without contralateral stenosis). Patients were excluded if they had intracranial hemorrhage or other types of stroke as large-artery atherosclerosis, cardioembolic, cryptogenic stroke, stroke of other determined etiology. Patients with silent white matter disease only without actual infarcts, patients who had rTPA were also excluded. All patients were subjected to complete history taking including personal data, past history and risk factors, detailed history of current illness, complete clinical picture and drug history, general and neurological examination. Stroke severity was assessed by National Institutes of Health Stroke Scale (NIHSS) on admission and discharge [5]. The modified Rankin Scale (mRS) was assessed on discharge and 3 months later to follow up their prognosis [6]. MRI protocol was performed, to investigate regional variations in perfusion in both grey matter and white matter. All patients were examined using a 1.5-T MR scanner (Achieva and Ingenia, Philips medical system, Eindhoven, Netherlands). To give the patients contrast, an 18- or 20-gauge IV catheter was inserted in the antecubital fossa before scanning. During the first run of a standard dose (0.1 mmol/kg) bolus of gadopentetate dimeglumine, a series of 60 DSCMRI pictures were taken at 1-s intervals. Absolute perfusion parameters such as cerebral blood volume (CBV), cerebral blood flow (CBF), and time to peak (TTP) were calculated by standard algorithms [7]. Carotid duplex was conducted to detect internal carotid stenosis, and transcranial color-coded duplex (TCCD) using phase array 2.4 Hz probe for evaluation of vasomotor reactivity (VMR) by measuring breath holding index (BHI). BHI = {[mean flow velocity (MFV) at the end of breath-holding- resting MFV]/resting MFV} × (100/seconds of breath-holding) [8]. VMR was assessed twice, first upon admission and second time 3 months after discharge.

Statistical analysis

Data analysis was done using IBM SPSS software package version 25.0 (Armonk, NY: IBM Corp). The normality test was done using Kolmogorov–Smirnov test. Quantitative data were described in mean and standard deviation in normally distributed variables and median and range and inter quartile range (IQR) in non-normally distributed ones and investigated using t test and Mann–Whitney U test, respectively, while qualitative data were described in frequency and percentage and tested with Chi-square test. Wilcoxon signed-rank test was used in the comparison of 2 related samples. Spearman correlation coefficient was used to evaluate the correlation between different variables. The significance of the obtained results was judged at $P < 0.05$.

Results

This study included 16 (53.3%) males and 14 (46.7%) females in lacunar infarction group in addition to 17 (56.7%) males and 13 (43.3%) females in the IBZ infarction group. The age of patients of the whole sample ranged from 48 to 85 years, with a mean age of 63.47 ± 7.637 in lacunar group and 61.30 ± 13.483 in the IBZ group. Most of patients had dyslipidemia (80% in lacunar group and 86.7% in border zone group), hypertension (63.3% in lacunar group and 57.7% in border zone group), while the least common risk factor was ischemic heart disease (13.3% in lacunar group and 26.7% in border zone group. There was no significant difference between groups as regards age, risk factors and number of risk factors (Table 1).

Comparing the severity of clinical presentation on admission using NIHSS, it was found that patients with border zone infarction had higher disability than patients with lacunar infarction: median NIHSS (IQ) 12 [6] vs. 7 [6], respectively, ($p = 0.001$) and on discharge 10 (5.25) vs. 4 [4], respectively, ($p < 0.001$). Although having different

Table 1 Demographic data, risk factors and laboratory findings

	Lacunar stroke $n=(30)$		Border zone stroke $n=(30)$		*T* test/Mann–Whitney $U^{\wedge}$/Chi test$^{\tau}$	
	Mean/frequency	SD/percentage	Mean/frequency	SD/percentage	$t/z^{\wedge}/x^{\tau}$	P
Age	63.47	7.637	61.30	13.483	0.766	0.448
Gender						
Female	14	46.7%	13	43.3%	0.067$^{\tau}$	0.795
Male	16	53.3%	17	56.7%		
n of vascular risk factors						
1	5	16.7%	1	3.3%	4.865 $^{\tau}$	0.301
2	8	26.7%	11	36.7%		
3	10	33.3%	13	43.3%		
4	6	20.0%	3	10.0%		
5	1	3.3%	2	6.7%		
IHD	4	13.3%	8	26.7%	1.667$^{\tau}$	0.197
Smoking	13	43.3%	12	40.0%	0.069$^{\tau}$	0.793
Diabetes	14	46.7%	15	50.0%	0.067$^{\tau}$	0.796
HTN	19	63.3%	17	56.7%	0.278$^{\tau}$	0.598
Dyslipidemia	24	80%	26	86.7%	0.480$^{\tau}$	0.488
Cholesterol (median, range)	200.00	110–300	184.00	99–345	− 0.903$^{\tau}$	0.367
Triglycerides (median, range)	141.00	101–323	150.00	70–427	− 0.466^	0.641
LDL (median, range)	119.50	84–163	108.50	50–222	− 0.954^	0.340
HDL (median, range)	44.00	30- 68	42.50	30–64	− 1.133^	0.257
HBA1C (median, range)	8.00	5–11.5	6.05	4.9–12	− 0.903^	0.367

Dyslipidemia is considered if LDL > 130, HDL < 40, triglycerides > 150, cholesterol > 200, HBA1c (4.5–5.6)

IHD ischemic heart disease, *HTN* hypertension, *LDL* low density lipoproteins, *HDL* high density lipoproteins, *SD* standard deviation

$^{\tau}$ Chi test is used

^Mann–Whitney *U* test is used

severity of disability (NIHSS) on admission, yet on measuring within-group improvement, both groups improved significantly on discharge ($p \leq 0.001$ in each group). However, inter-group comparison showed that lacunar group still had more significant improvement than IBZ group ($p=0.001$) (Table 2).

Table 2 Comparison of NIHSS and mRS between lacunar infarctions and borderzone infarctions

	Lacunar stroke $n=(30)$		Border zone stroke $n=(30)$		Mann–Whitney *U* test/Chi test$^{\tau}$		Wilcoxon signed ranks test	
	Median/frequency	IQR/percentage	Median/frequency	IQR/percentage	z/x^{τ}	*P*	Lacunar stroke	Border zone stroke
NIHSS Baseline	7	6	12	6	− 3.255	**0.001**	**< 0.001**	**< 0.001**
NIHSS Discharge	4	4	10	5.25	− 4.508	**< 0.001**		
Δ NIHSS	-3	1.25	− 2	1.25	− 4.411	**< 0.001**		
mRS Discharge ≤ 2	27	89.9%	11	36.7%	20.979$^{\tau}$	**< 0.001**		
mRS_3ms ≤ 2	29	96.7%	16	53.3%	25.546$^{\tau}$	**< 0.001**		
mRS Discharge (median/range)	1	0–3	3	0–4	− 4.442	**< 0.001**	**< 0.001**	**0.020**
mRS_3ms (median/range)	1	0–3	2	0–5	− 4.774	**< 0.001**		
Δ mRS	0	− 2–0	0	− 1–1	− 0.618	0.536		

The bold values mean that they are significant regarding P value (statistically significant)

NIHSS National Institutes of Health Stroke Scale, *mRS* modified Rankin scale, *3 ms* 3 months follow-up, Δ: difference

$^{\tau}$ Chi test is used

As for good outcome (mRS $\leq$ 2) on discharge, 89.9% of lacunar group showed good outcome, vs. 36.7% of IBZ group ($p \leq 0.001$). At 3 months follow-up, 96.7% of the lacunar group had a good outcome vs. 53.3% of the IBZ group ($p \leq 0.001$).

It is worth mentioning that within-group comparison showed significant improvement after 3 months ($p \leq 0.001$) in lacunar stroke compared to ($p = 0.02$) in IBZ (Table 2).

By investigating VMR in both groups, 56.7% of patients with lacunar stroke had impaired reactivity vs. 100% of patients in IBZ group ($p < 0.001$). At 3 months follow-up, this number dropped to 23.3% in lacunar group, but persisted as 100% in IBZ group ($p < 0.001$).

There was statistically significant impairment in all parameters in patients with IBZ infarction than patients with lacunar infarction which means longer TTP, decreased CBF and CBV ($p < 0.001$, 0.001, 0.023, respectively).

Logistic regression for the lacunar group showed a negative correlation between VMR at baseline and after 3 months with NIHSS (rho = -0.540, $p = 0.002$, rho = − 0.636, $p < 0.001$, respectively), which denotes that good VMR correlated with less stroke severity.

There was also a positive statistically significant correlation between inter-side difference CBF and NIHSS (rho = 0.399, $p = 0.029$), which means that reduced CBF was associated with severer stroke. Three months later mRS did not show significant correlation with any of the studied parameters.

On the other hand, logistic regression analysis for IBZ group could not be performed for VMR since 100% of patients were impaired. Therefore, logistic regression was performed for MRI perfusion parameters vs. degree of stenosis and showed a positive statistically significant correlation between inter-side difference TTP and CBF with degree of stenosis (rho = 0.501, $p = 0.005$, rho = 0.421, $p = 0.021$, respectively), denoting that reduced flow is associated with higher stenosis. While no correlation was detected for CBV. There was also no significant correlation between MRI perfusion parameters vs. NIHSS and mRS.

Discussion

In the current study, both IBZ infarctions and lacunar infarctions shared the same risk factors leading to atherosclerosis, whether small vessel or large vessel atherosclerosis, which is key factor in their pathogenesis. Atherosclerosis can cause many changes in the arterial wall leading to obstruction of proximal lumen. If the occlusion occurred in perforating arterioles smaller than 50 µm in diameter, lacunar infarctions will result [9], while if it occurred in leptomeningeal vessels and carotid arteries together with systemic hypotension, it would result in ischemic lesions situated along the watershed zones [10]. Additionally, both disorders share the MRI picture of white matter lesions that might occur bilaterally whether symmetrical or non-symmetrical. So, we aimed to differentiate between these 2 types of ischemic stroke because IBZ infarction can be misdiagnosed as SVD especially if it occurred bilaterally causing white matter lesions on MRI. In this study, the frequency of vascular risk factors in a descending order in both groups; dyslipidemia, hypertension, diabetes, smoking and IHD, and even the glycemic level did not differ significantly between groups. Similarly, many studies reported dyslipidemia to be the commonest risk factor [11, 12], while others stated that hypertension was the commonest [13].

Regarding clinical disability, on comparing NIHSS and mRS of the 2 groups, IBZ group had higher NIHSS on admission than lacunar group. At 3 months follow-up both groups showed significant improvement of mRS than on admission, yet IBZ group showed significantly less improvement than lacunar group. Likewise, bad prognosis of IBZ infarctions and good prognosis of lacunar infarctions were described by many studies [14, 15]. On admission, VMR was impaired in more than half of the patients in the lacunar group and in all those in the IBZ group. At 3 months follow-up 33.4% of patients improved in the lacunar group while impairment persisted in all patients of IBZ group. This agrees with many other studies who stated that perfusion reserve and VMR were dramatically reduced in patients complaining of carotid artery occlusions [16, 17]. In another study, VMR was related to early neurological deterioration in patients with lacunar infarction [18], white matter hyperintensities also were associated with less cerebral blood flow and more impairment of VMR than normal brain tissue, moreover it was reported that reduced VMR can predict progression from normal white matter to white matter hyperintensities in small vessel disease [19]. The current study suggests that VMR impairment in lacunar group is significantly correlated with severer stroke on presentation. However, we were not able to perform a correlation analysis between VMR and clinical severity in IBZ group as all the patients showed VMR impairment.

On comparing the 3 parameters (TTP, CBF, and CBV) between the 2 groups, impairment in all parameters was more in IBZ infarction than in lacunar infarction which means longer TTP, decreased CBF and CBV. This agrees with various studies stating that ICA stenosis causes hemodynamic disturbance thus causing more impairment in MRI perfusion parameters [3, 20]. We could also detect a correlation between inter-side difference of TTP and CBF with degree of stenosis, as the degree of stenosis increased, blood flow decreased ipsilaterally and the difference in TTP and CBF between the 2 hemispheres increased. Yet no such correlation was detected with CBV, mostly because CBV in some cases may actually show increased value to maintain cerebral auto regulation [21]. A previous study of CT perfusion in ICA occlusion found that CBF was not significantly different from that of the contralateral hemisphere, whereas ipsilateral CBV and TTP were in comparison with those in the contralateral hemisphere, substantially higher [20]. Meanwhile we identified a significant correlation between an increased inter-side difference CBF and stroke severity in lacunar group; other studies employed different elements of measurement as mean transit time (MTT) to reach the same correlation [22]. No significant correlation was found between VMR and MRI perfusion parameters in lacunar infarcts mostly due to absence of severe hemodynamic instability, unlike that which results from carotid stenosis in cases of IBZ infarction [23].

The study had some limitations as MRI brain perfusion could have been preferably repeated at 3 months follow-up and compared with the initial MRI to test for the possibility of recanalization and its effect on perfusion and prognosis. However, that was not feasible due to limited resources.

Conclusion

Although IBZ infarctions can simulate the MRI picture of multiple lacunar infarcts, yet the presence of severe impairment of VMR or reduced perfusion in white matter lesions is more in favor of IBZ infarction. Therefore, patients with IBZ infarctions tend to have worse prognosis and higher clinical disability.

Abbreviations

BHI: Breath holding index; CBF: Cerebral blood flow; CBV: Cerebral blood volume; CSVD: Cerebral small vessel disease; IBZ: Internal border zone infarction; MFV: Mean flow velocity; MRI: Magnetic resonance imaging; mRS: Modified Rankin Scale; MTT: Mean transit time; NIHSS: National Institutes of Health and Stroke Scale; TCCD: Trans-cranial color-coded duplex; TTP: Time to peak; VMR: Vasomotor reactivity.

Acknowledgements

Not applicable.

Author contributions

SH: data collection and research project execution. MF: contribution to the concept and design, drafting the manuscript. AA: conception of the work, manuscript revision. ED: acquisition of data and analysis of data, EH: analysis and interpretation of data. HA: conception of the work, Approved the version to be published. NE: Conception and design, revised the manuscript critically for important intellectual content. All authors have agreed to conditions noted on the Authorship Agreement Form and have read and approved the final version submitted. The content of the manuscript has not been published, or submitted for publication elsewhere. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non profit sectors.

Availability of data and materials

All raw data will be available on the editor request through communication with the corresponding author.

Declarations

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the faculty of medicine, Ain Shams university research and ethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from participants for participation. We obtained approval from research ethics committee No. FWA 000017585. On 5/5/2019.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Neurology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt. [2]Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Received: 9 June 2022 Accepted: 11 August 2022
Published online: 27 August 2022

References

1. Yulu S, Joanna M. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke Vasc Neurol. 2016;1(3):83–92.
2. Mangla R, Kolar B, Almast J, Ekholm S. Border zone infarcts: pathophysiologic and imaging characteristics. Radiographics. 2011;31(5):1201–14.
3. El Nahas NM, Aref HM, Alloush TK, Fahmy NA, Ahmed KA, El Basiouny AA, et al. Borderzone infarction and small vessel disease in a sample of egyptian stroke patients: differences and similarities. Neurol India. 2021;69(3):670–5.
4. Venkataraman P, Tadi P, Lui F. Lacunar Syndromes. In: StatPearls [Internet]. Treasure Island (FL): StatPearls; 2022. PMID: 30480945.
5. Hage V, The NIH. Stroke scale: a window into neurological status. Nurs Spectr. 2011;24:44–9.
6. Saver J, Filip B, Hamilton S, Yanes A, Craig S, Cho M, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA)". Stroke. 2010;41(5):992–5.
7. Isaka Y, Nagano K, Narita M, Ashida K, Imaizumi M. High signal intensity on T2-weighted magnetic resonance imaging and cerebral hemodynamic reserve in carotid occlusive disease. Stroke. 1997;28(2):354–7.
8. Forbes T. Angioplasty, various techniques and challenges in treatment of congenital and acquired vascular stenosis, 5th edition. InTech; 2012; p. 9–30.
9. Kraft P, Schuhmann MK, Garz C. Hypercholesterolemia induced cerebral small vessel disease. PLoS ONE. 2017. https://doi.org/10.1371/journal.pone.0182822.
10. Torvik A. The pathogenesis of watershed infarcts in the brain. Stroke. 1984;15(2):221–3.
11. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761–75.
12. Mathiesen EB, Joakimsen O, Bonaa KH. Prevalence of and risk factors associated with carotid artery stenosis: the Tromso study. Cerebrovasc Dis. 2001;12(1):44–51.
13. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart association. Circulation. 2011;123:e18–209.
14. Li Y, Li M, Zhang X, Yang S, Fan H, Qin W, et al. Clinical features and the degree of cerebrovascular stenosis in different types and subtypes of

cerebral watershed infarction. BMC Neurol. 2017. https://doi.org/10.1186/s12883-017-0947-6.
15. Donnan G, Norrving B, Bamford J, Bogousslavsky J. Prognosis of patients with lacunar infarction syndromes subcortical stroke. 2nd ed. Oxford: Oxford Medical Publications; 2002. p. 297–309.
16. Afify H, Helmy SM, El-Nabil LM, Elkhayat N, El Nahas NM, Zakaria M. Cerebral vasomotor reactivity in border zone infarcts; a transcranial Doppler study. Egypt J Neurol Psychiatry Neurosurg. 2019;55:50.
17. Weiller C, Ringelstein EB, Reiche W, Buell U. Clinical and hemodynamic aspects of low-flow infarcts. Stroke. 1991;22(9):1117–23.
18. Lee MJ, Moon S, Cho S, Chung JW, Seo WK, Bang OY, et al. Mechanisms involved in lacunar infarction and their role in early neurological deterioration. J Neurosonol Neuroimag. 2020;12(1):26–32.
19. Shi Y, Thrippleton MJ, Blair GW, Dickie DA, Marshall I, Hamilton I, et al. Small vessel disease is associated with altered cerebrovascular pulsatility but not resting cerebral blood flow. J Cereb Blood Flow Metab. 2020;40(1):85–99.
20. Cheng XQ, Tian JM, Zuo CJ, Liu J, Zhang Q, Lu GM. Quantitative perfusion computed tomography measurements of cerebral hemodynamics: correlation with digital subtraction angiography identified primary and secondary cerebral collaterals in internal carotid artery occlusive disease. Eur J Radiol. 2012;81:1224–30.
21. Siemund R, Cronqvist M, Andsberg G, Ramgren B, Knutsson L, Holtås S. Cerebral perfusion imaging in hemodynamic stroke: be aware of the pattern. Interv Neuroradiol. 2009;15(4):385–94.
22. Yamada M, Yoshimura S, Kaku Y, Iwama T, Watarai H, Andoh T, et al. Prediction of neurologic deterioration in patients with lacunar infarction in the territory of the lenticulostriate artery using perfusion ct. Am J Neuroradiol. 2004;25(3):402–8.
23. Müller M, Voges M, Piepgras U, Schimrigk K. Assessment of cerebral vasomotor reactivity by transcranial Doppler ultrasound and breath-holding. A comparison with acetazolamide as vasodilatory stimulus. Stroke. 1995;26:96–100.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.